UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ORTHO-MCNEIL PHARMACEUTICAL, INC., ORTHO-MCNEIL, INC., and DAIICHI SANKYO CO., LTD.	:	
Plaintiffs,	:	Civ. Action No. 06-4999 (GEB) (TJB)
v.	:	
LUPIN PHARMACEUTICAL, INC. and LUPIN LTD.	:	
Defendants.	:	

PLAINTIFFS' MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT AND IN SUPPORT OF PLAINTIFFS' CROSS-MOTION FOR SUMMARY JUDGMENT

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Plaintiffs Ortho-McNeil Pharmaceutical, Inc., Ortho-McNeil, Inc. ("Ortho") and Daiichi Sankyo Company, Ltd. ("Daiichi Sankyo" and together with Ortho, "Plaintiffs"), submit this memorandum in opposition to the motion for summary judgment by Defendants Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") and in support of Plaintiffs' cross-motion for summary judgment. For the reasons discussed below, Plaintiffs respectfully request that the Court find as a matter of law that the United States Patent & Trademark Office ("PTO") and Food & Drug Administration ("FDA") correctly concluded that U.S. Patent No. 5,053,407 (the "'407 patent") is entitled to a patent term extension.

Lupin's attempt to overturn the decision to grant a patent term extension for the '407 patent should be rejected as a matter of law. As an initial matter, the decision of the PTO – made after obtaining input from the FDA – is presumed to be valid and is entitled to great deference. Lupin has failed to offer clear and convincing evidence – as it must do – that the PTO and FDA acted arbitrarily, capriciously, abused their discretion or acted otherwise not in accordance with law. To the contrary, there is far more than the requisite "rational basis" for the agencies' decisions – they are both fully consistent with the longstanding practices of the agencies and industry, and are strongly supported by the undisputed science.

First, based on the judicially approved and adopted construction of the '407 patent (which Lupin does not challenge here), the product claimed in the '407 patent – levofloxacin that is optically active and substantially optically pure – was not present in the previously approved Floxin®. As the product claimed in the '407 patent was first approved in Levaquin®, it meets all of the requirements necessary for a patent term extension. *See infra* at Argument, Part II.

Second, the PTO and the FDA acted in a manner consistent with their regular and longstanding practices in granting the term extension of the '407 patent. In dozens of prior instances in which the FDA has approved racemates, the FDA has characterized the "active ingredient" in the racemic product as the racemate itself, not one or both of its enantiomers. Likewise, when considering at least five other applications for patent term extensions for patents covering enantiomeric products subsequent to approval of their corresponding racemates, the PTO, informed by the expertise of the FDA, has determined that the patents were entitled to term extensions. In each instance, the FDA concluded that approval of the racemate did not constitute prior approval of the same active ingredient as in the enantiomeric product. *See infra* at Argument, Part III.A.

Third, the decisions of the PTO and the FDA also are rooted in, and entirely consistent with, industry custom, including Lupin's own practices. The standard manufacturing process used throughout industry for small molecule

pharmaceuticals involves two phases, the first of which results in the production of the "active ingredient," which is then blended with excipients in the second manufacturing phase to create the finished drug. Here, the end product of the first phase in the production of Floxin® is ofloxacin, whereas the end product of the same phase in the production of Levaquin® is levofloxacin. *See infra* at Argument, Part III.B.1.

Finally, from the clinical, pharmacology, microbiology and medicinal chemistry perspectives, ofloxacin and levofloxacin are entirely different therapeutic agents and, therefore, properly are considered to be different active ingredients. *See infra* Part III.B.2.

Lupin's contention that levofloxacin is somehow indistinguishable from racemic ofloxacin was the premise of the anticipation and obviousness arguments previously advanced by Mylan (and others) and appropriately rejected by each court to consider these issues. *See Ortho-McNeil Pharmaceutical Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713 (N.D.W. Va. 2004), *aff'd*, 161 Fed. Appx. 944 (Fed. Cir. 2005). Lupin's efforts here should meet the same fate.

FACTUAL BACKGROUND

I. Invention of Ofloxacin and Levofloxacin

After years of research, Daiichi Pharmaceutical Company, Ltd. (predecessor to Daiichi Sankyo, hereinafter "Daiichi") synthesized ofloxacin, a

new quinolone anti-infective, for which it obtained U.S. Patent No. 4,382,892 ("the '892 patent") in 1983. In December 1990, the FDA approved Ortho's New Drug Application for Floxin®, which, as its FDA-approved labeling and its Orange Book entry confirm, contains a single active ingredient: ofloxacin. *See* Paragraph 1 of "Plaintiffs' Statement of Undisputed Facts Under L. Civ. R. 56.1 in Support of Their Cross-Motion for Summary Judgment Pursuant to Fed. R. Civ. P. 56" (hereinafter "PF ¶ __") (Declaration of David Lin ("Lin") ¶ 25 & Ex. F thereto).

Ofloxacin is a racemate, which is a material containing equal amounts of two "optical isomers" or "enantiomers," molecules that are identical except for the orientation or their atoms in space.[1] *See* PF ¶ 2 (Declaration of Mark P. Wentland ("Wentland") ¶ 15). Chemists distinguish enantiomers through their "optical activity" – *i.e.*, by the direction in which they rotate a plane of polarized light. *See* PF ¶ 3 (Wentland ¶ 21). If the enantiomer rotates plane-polarized light to the right, or in a clockwise direction, the enantiomer is "dextrorotatory," which is indicated by a "(+)"; alternatively, if the enantiomer rotates plane-polarized light to the left, or counter-clockwise, it is "levorotatory," which is indicated by a "(–)". *See* PF ¶ 4 (Wentland ¶ 21). Chemists also distinguish optical isomers more

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[1] Plaintiffs use the terms "optical isomers" and "enantiomers" synonymously in this memorandum.

directly based on the spatial orientation of their atoms, using nomenclature designations such as "S" and "R." *See* PF ¶ 5 (Wentland ¶ 22). Racemates are optically inactive – *i.e.* they do not rotate a plane of polarized light – and are indicated by a "(±)" or "(RS)" symbol or the absence of any symbol. *See* PF ¶ 6 (*Mylan*, 348 F. Supp. 2d at 721).

Ofloxacin was not an optimal anti-infective. *See* PF ¶ 7 (Declaration of George G. Zhanel ("Zhanel") ¶ 32). It had reduced efficacy against *Streptococcus pneumoniae*, a major bacterial pathogen; caused central nervous system side effects which limited its ability to be dosed at a sufficiently high level to kill certain bacteria; and had limited solubility and other problems. *See* PF ¶ 8 (Zhanel ¶¶ 29, 33, 34, 55, 56).

Daiichi spent years searching for a better quinolone. Between 1980 and 1985, Daiichi researchers synthesized hundreds of compounds, screened them for activity, solubility and toxicity, and compared the results to the known profiles of ofloxacin and ciprofloxacin. Daiichi scientists also made a number of unsuccessful attempts to separate ofloxacin into its constituent enantiomers. *See* PF ¶ 9 (Wentland ¶ 31). Despite their doubts that the ofloxacin enantiomers would be significantly more effective than ofloxacin itself, Daiichi researchers nonetheless attempted to obtain them. *See Mylan*, 348 F. Supp. 2d at 754.

Daiichi never managed to separate ofloxacin into its enantiomers. *See* PF ¶ 10 (Wentland ¶ 31). In 1985, after four years of failure, Daiichi eventually succeeded in synthesizing levofloxacin using novel synthesis routes rather than obtaining it from racemic ofloxacin. *See* PF ¶ 11 (Wentland ¶ 32). Upon doing so, the Daiichi researchers learned that the substantially optically pure levorotatory enantiomer – the S(–) enantiomer substantially free of R(+) molecules – or levofloxacin, was approximately twice as active as racemic ofloxacin, the maximum possible difference in activity between an enantiomer and its racemate. *See* PF ¶ 12 (*Mylan*, 348 F. Supp. 2d at 751, 754). They also learned that levofloxacin was ten times more water-soluble than ofloxacin, and less toxic than ofloxacin. *See* PF ¶ 13 (Declaration of Allan S. Myerson ("Myerson") ¶ 22; Zhanel ¶ 55; *Mylan*, 348 F. Supp. 2d at 751, 754). With its combination of superior antimicrobial activity, increased solubility and lower toxicity than ofloxacin, levofloxacin was a breakthrough, "pharmaceutically superior to ofloxacin in virtually every relevant aspect." *Mylan*, 348 F. Supp. 2d at 754. Levofloxacin turned out to be a totally different and dramatically better drug.

II. Patenting and Approval of Levofloxacin

On June 20, 1986, Daiichi filed the U.S. patent application that ultimately issued as the '407 patent. *See* PF ¶ 14 (Declaration of Karen A. Confoy ("Confoy"), Exhibit F). The PTO initially rejected the claims as obvious in view

of – though, not anticipated by – ofloxacin. *See* PF ¶ 15 (Declaration of Noah M. Leibowitz ("Leibowitz"), Exhibit A (file history excerpts) at JA9094-99; *Mylan*, 348 F. Supp. 2d at 743). However, after considering the unexpected benefits of levofloxacin over ofloxacin, the PTO allowed the claims. *See* PF ¶ 16 (Leibowitz, Exhibit A at JA9238-9245 and 9441; *Mylan*, 348 F. Supp. 2d at 743). Following an interference proceeding containing a count directed to "[a]n enantiomerically pure . . . acid and derivatives thereof [that are] antibacterially more active than [their] racemates," the Board of Patent Appeals and Interferences granted judgment to Daiichi, *see* PF ¶ 17 (Leibowitz, Exhibit A at JA9319 & JA9323; *Mylan*, 348 F. Supp. 2d at 732), and the '407 patent issued on October 1, 1991.[2]

Claim 2 of the '407 patent is directed to an "S(–)" compound whose common name is levofloxacin. *See* PF ¶ 18 (Confoy, Exhibit F). Claim 5 is directed to a process for treating a patient with "an antimicrobially effective

[2] A patent interference is a proceeding that decides the issue of priority of invention between two or more parties who claim the same patentable invention. Such a proceeding is declared after an examiner determines that the patent applications of both parties contain allowable and patentable claims. The "count" of the interference is the broadest patentable claim of either party that circumscribes the interfering subject matter.

amount" of the same compound.[3] *See* PF ¶ 19 (Confoy, Exhibit F). These claims were construed by Chief Judge Irene Keeley of the Northern District of West Virginia to refer to optically active and substantially optically pure levofloxacin. *See* PF ¶ 20 (*Mylan*, 348 F. Supp. 2d at 728-30). This Court also adopted that claim construction in granting Plaintiffs' summary judgment against several other ANDA challengers in *Ortho-McNeil Pharm. Inc. v. Teva Pharms. USA* (Civil Action No. 02-2794) (Brown, C.J.). *See* PF ¶ 21. Lupin does not challenge the patentability of levofloxacin, nor the construction of claims 2 and 5 of the '407 patent as describing optically active and substantially optically pure levofloxacin. *See* PF ¶ 22 (Confoy, Exhibit A). As construed, claims 2 and 5 necessarily exclude ofloxacin as well as any individual S(–) molecules that may be present in ofloxacin because racemic ofloxacin, which contains an equal number of S(–) and R(+) molecules, is optically inactive and optically impure. *See* PF ¶ 23 (*Mylan*, 348 F. Supp. 2d at 726-29).

In 1996, the FDA approved Levaquin®, which is marketed by Ortho. Its FDA-approved labeling, as well as the Orange Book, identify Levaquin® as

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[3] Although neither claim includes the word "compound," each is dependent upon another claim that uses that word: claim 2 from claim 1, and claim 5 from claim 4.

containing a single active ingredient: levofloxacin. *See* PF ¶ 24 (Lin ¶ 25 & Ex. G thereto).

III. Grant of Patent Term Extension

As part of the Hatch-Waxman Act, Congress amended the Patent Act to afford certain patents a term extension to compensate the patentee for time spent obtaining regulatory approval for the sale of products covered by the patent. *See, e.g.*, 35 U.S.C. §§ 155-156. Congress believed that, where a patentee must obtain regulatory approval before marketing a product covered by the patent (as with pharmaceuticals, which must be approved by the FDA), the patent term should be extended to ensure that there is a sufficient patent term remaining after the product comes to market to protect the patentee's investment in innovation. *See* 130 Cong. Rec. S10504 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch) ("[Congress sought to] restore to our domestic drug companies some of the incentive for innovation which has weakened as Federal pre-market approval requirements have become more expensive and time consuming.").

A decision on whether a U.S. patent should be extended under the Hatch-Waxman provisions, and for how long, involves both the PTO and FDA acting in concert to evaluate the merits of an extension request. *See* PF ¶ 25 (Declaration of Gerald J. Mossinghoff ("Mossinghoff") ¶ 10). The PTO and the FDA do so pursuant to a Memorandum of Understanding ("MOU") that sets forth

the formal procedures to be followed to ensure that a patent meets all of the qualifications for extension. *See* PF ¶ 26 (Mossinghoff ¶ 10; Lin ¶ 24).

On February 18, 1997, Daiichi submitted to the PTO an application for term extension of the '407 patent. *See* PF ¶ 27 (Mossinghoff ¶ 11). As part of this application, Daiichi specifically informed the PTO that Floxin® had been previously approved by the FDA and that the term of the '892 patent covering racemic ofloxacin had been previously extended. *See* PF ¶ 28 (Mossinghoff ¶ 11). Pursuant to the MOU, the PTO sent the term extension application to the FDA, indicating that the patent "would be eligible for extension of the patent term under 35 U.S.C. § 156 if the approval of Levaquin® is the first permitted marketing or use of the active ingredient thereof," and requesting confirmation of the same. *See* PF ¶ 29 (Mossinghoff ¶ 12; Lin ¶ 27). The letter from the PTO further informed the FDA that "[a]pplicant has stated that the 'corresponding racemate Floxin' has been previously approved." *See* PF ¶ 30 (Mossinghoff ¶ 12).

On July 18, 1997, the FDA sent a letter to the PTO, stating that

> A review of the Food and Drug Administration's official records indicates that this product [Levaquin®] was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp[.] 1224 (E.D. Va. 1989), aff'd 894 F.2d 392 (Fed. Cir. 1990).

See PF ¶ 31 (Mossinghoff ¶ 13; Lin, Ex. H) (emphasis added).

After additional correspondence between the PTO and the FDA established the length of the regulatory review period and the corresponding length of the patent term extension, on August 4, 1999, the PTO granted the requested patent term extension. *See* PF ¶ 32 (Mossinghoff ¶¶ 14-18).

ARGUMENT

Summary judgment is appropriate only "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). When ruling on a motion for summary judgment, all of the nonmovant's evidence is to be credited, and all justifiable inferences are to be drawn in the nonmovant's favor. *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1384 (Fed. Cir. 2004); *Caterpillar Inc. v. Deere & Co.*, 224 F.3d 1374, 1379 (Fed. Cir. 2000).

I. Lupin Cannot Show by Clear and Convincing Evidence That the FDA and PTO Acted Arbitrarily and Capriciously

Lupin cannot prevail on its motion for summary judgment as a matter of law. As discussed below, Lupin cannot show – and has made no attempt to show – that the "product" claimed in the '407 patent was also in Floxin®. Claims 2 and 5 of the '407 patent have been construed in prior litigation as describing optically active and substantially optically pure levofloxacin. Lupin has not

challenged this construction here, and therefore cannot, and does not, contend that Floxin® contains what is claimed in the '407 patent. For the same reason, Plaintiffs' cross-motion for summary judgment should be granted.

In the event the Court were to entertain the merits of Lupin's motion and consider whether levofloxacin was an "active ingredient" in Floxin®, the Court would need to view "the evidence presented [by Lupin] through the prism of the substantive evidentiary burden." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 254 (1986); *see Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 872 (Fed. Cir. 1991). In this case, the burden of proof facing Lupin, and the difficulties it faces in attempting to meet that burden, are especially formidable. Correlatively, the difficulties facing Plaintiffs are relatively light, and are easily met here.

First, the "presumption of validity applies to the PTO's determination to grant a patent term extension." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 511 (D. Del. 2005) (emphasis added), *rev'd in part on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006). To overcome this presumption, Lupin must affirmatively advance clear and convincing evidence that the PTO's extension of the term of the '407 patent was not valid. *See Pfizer*, 457 F.3d at 1291 (agreeing with the District Court that "Ranbaxy failed to establish by clear and convincing evidence that the term extension was invalid"); *see also* 35 U.S.C. § 282 (noting

that invalidity of a patent term extension "shall be a defense in any action involving the infringement of a patent during the period of the extension of its term and shall be pleaded"). Clear and convincing evidence exists when the movant "place[s] in [the mind of] the ultimate factfinder an abiding conviction that the truth of its factual contentions are 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984).

Second, Lupin is seeking to overturn an agency determination, which – as Lupin admits, *see* Lupin Mem. at 12 – can be done only if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *see Fertilizer Institute v. Browner*, 163 F.3d 774, 777 (3d Cir. 1998); *Fund for Animals, Inc. v. Rice*, 85 F.3d 535, 541 (11th Cir. 1996).[4] Here, the PTO's grant of the patent term extension was informed by the FDA, which advised the PTO that the approval of Levaquin® "represents the first permitted

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[4] Lupin has not cited, and Plaintiffs have not found, any case holding that a party must show that the PTO acted arbitrarily and capriciously to overturn a patent term extension. Plaintiffs note, however, that this standard has been applied in other settings involving PTO determinations. *See Ray v. Lehman*, 55 F.3d 606, 608 (Fed. Cir. 1995). In any event, as explained herein, the Federal Circuit has held that a party challenging a patent term extension can prevail only by showing invalidity of the extension by clear and convincing evidence, and that great deference must be accorded the PTO when considering such a challenge. Lupin cannot possibly meet its burden here, irrespective of whether it must show that the PTO acted arbitrarily and capriciously.

commercial marketing or use of the product." *See* PF ¶ 31 (Mossinghoff ¶ 13). This case is therefore one in which not just one, but two different agencies – both charged with making determinations regarding eligibility for patent term extension – have affirmatively concluded that the '407 patent is entitled to term extension.

Lupin therefore can succeed only if it can show by clear and convincing evidence that the PTO and the FDA acted arbitrarily, capriciously, abused their discretion, or acted "otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). To overcome this formidable burden, Lupin seeks to characterize the issue presented here as one of erroneous interpretation of the statute. *See* Lupin Mem. at 12 ("An abuse of discretion occurs when a decision is based on an erroneous interpretation of the law."). As demonstrated below, however, this case concerns not an issue of statutory construction – as Lupin itself admits, the patent term extension provisions have an ordinary plain meaning and, to the extent necessary, have already been construed – but application of an accepted statutory construction to a set of highly complex scientific facts. Under these circumstances, Lupin cannot meet its burden. Moreover, Lupin has provided the Court with no reason to second-guess the expert determinations of the PTO and the FDA, and summary judgment in favor of Plaintiffs therefore should be granted.

A close examination of Lupin's arguments readily demonstrates that this case concerns an agency's application of a statute to facts, not an agency's

interpretation of that statute. Nowhere does Lupin identify any particular statutory "construction" or "interpretation" that it seeks from the Court.[5] Instead, Lupin concedes that the term "active ingredient" is "well-defined," having received extensive treatment in *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990), which the parties agree is authoritative and binding precedent in this case. *See* Lupin Mem. at 15.[6] Additionally, both Lupin and Plaintiffs agree that the issue of whether the previously approved Floxin® product contained the same active

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[5] Tellingly, Lupin does not cite to any legislative history addressing the treatment of enantiomers of previously approved racemates in the context of patent term extensions. The legislative history is understandably silent on this issue, given the extensive familiarity and experience of the FDA with the characterization of active ingredients, and the longstanding definition of that term by the FDA. By using such a well-defined regulatory term at the time of enactment of the statute, Congress was adopting that meaning for purposes of the statute. *See, e.g., Bragdon v. Abbott*, 524 U.S. 624, 631 (1998) ("Congress' repetition of a well-established term carries the implication that Congress intended the term to be construed in accordance with pre-existing regulatory interpretations.").

[6] Lupin appears to recognize *Glaxo* as controlling precedent in this case. To the extent it argues that the controlling definition is provided in *Pfizer, Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004), which equated "active ingredient" with "active moiety," that contention is unavailing. *Pfizer* concerned the scope of a patent holder's rights during the extension period as defined by 35 U.S.C. § 156(b), and did not address eligibility for such an extension under Section 156(a), which is at issue here. In any event, because *Pfizer* was a panel decision, it could not, under well-established Federal Circuit procedures, have overruled the earlier panel decision in *Glaxo*. *See Barclay v. U.S.*, 443 F.3d 1368, 1373 (Fed. Cir. 2006) ("Panels of this court are bound by previous precedential decisions [unless and] until overturned by the Supreme Court or by this court *en banc*."); Fed. Cir. R. 35(a)(1) ("only the court en banc may overrule a binding precedent").

ingredient as Levaquin® depends upon application of the FDA's longstanding definition of "active ingredient." *See* Lupin Mem. at 15-16 ("The well-defined, ordinary, common meaning of 'active ingredient' in 1984 was, as it remains today, 'any component that is intended to furnish pharmacological activity or other direct effect….") (quoting 21 CFR § 210.3(b)(7)); *see also Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1373 (Fed. Cir. 2003) (citing FDA definition of "active ingredient" as authoritative).

In short, the issue presented by these dueling motions is not one of statutory interpretation, but rather the application of the longstanding definition of "active ingredient" by the FDA when it approved the racemic product Floxin®: was it the levorotatory enantiomer of ofloxacin as opposed to racemic ofloxacin itself that was "intended to furnish pharmacological activity or other direct effect"? Clearly not, as it would no doubt come as a great surprise to the FDA that when it approved Floxin®, it was approving not only ofloxacin, but also levofloxacin, on which no clinical testing had been conducted and no data submitted as yet. For this reason, there can be no question of "erroneous interpretation of the law"; instead, the issue is merely whether the PTO and FDA acted arbitrarily and capriciously in determining that it was racemic ofloxacin – not levofloxacin – that was intended to furnish the pharmacological activity in Floxin® and therefore that levofloxacin, Levaquin®'s active ingredient, had not previously been approved.

In *Glaxo*, the Federal Circuit refused to defer to the PTO's interpretation of "product" as a "new chemical entity" in the patent term extension provisions, reasoning that Congress chose a particular term – "active ingredient" – to define "product," and that the PTO could not define "product" otherwise. *See* 894 F.2d at 399. For this reason, the court refused to defer to "the [PTO] Commissioner's surmise of Congress' intent in framing its definition," but forewarned that it would "give great deference to the Commissioner's determinations as to which patented chemical compounds fall within Congress' definition of 'products.'" *Id.* (emphasis added). Such deference is appropriate here as it is whenever Congress has delegated a scientific or technical determination to an agency. *See id.* ("[s]ignificant deference is due to an agency's technical expertise when Congress has explicitly or implicitly delegated to the agency the making of scientific determinations").[7] Later, in *Merck*, the Federal

[7] This principle is a cornerstone of federal administrative law. *See Nat'l Oilseed Processors Ass'n*, 924 F. Supp. 1193, 1201-02 (D.C. Cir. 1996) ("Where the agency decision turns on issues requiring the exercise of technical or scientific judgment, it is essential for judges to 'look at the decision not as a chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality.'") (citations omitted); *United States v. Alpine Land & Reservoir Co.*, 887 F.2d 207, 213 (9th Cir. 1989) ("Deference to an agency's technical expertise and experience is particularly warranted with respect to questions involving engineering and scientific matters.").

Circuit considered a challenge to the validity of a patent term extension and returned to the distinction it drew in *Glaxo* between the PTO's "determinations" as to which patented chemical compounds fall within the definition of "products" – which are entitled to great deference – and its "surmise" of Congressional intent – which is entitled to little or no deference: "We agree with the [PTO]'s determination, and with its implementation by the Food and Drug Administration." *Merck*, 347 F.3d at 1373-74.

Congress has delegated to the PTO – with substantial expert assistance from the FDA – the authority to make the highly technical determinations required under Section 156(a). The decisions of those agencies, accordingly, are entitled to great deference and the Court should not lightly substitute its judgment for that of the agencies. *See Ray*, 55 F.3d at 608. Indeed, so long as there was a rational basis for their determination, the Court cannot substitute its judgment for that of the PTO and FDA even if the Court disagrees with their decisions. *See Exxon Corp. v. FEA*, 398 F. Supp. 865, 879 (D.C. Cir. 1975); *Simeon Mgmt. Corp. v. FTC*, 579 F.2d 1137, 1142 (9th Cir. 1978). As set forth below, there is far more than a mere rational basis for the determinations of the PTO and the FDA in extending the term of the '407 patent. For this reason, Lupin's motion for summary judgment should be denied, and Plaintiffs' cross-motion granted.

II. Ofloxacin Does Not Contain the Product Claimed in the '407 Patent

Claims 2 and 5 of the '407 patent have been construed in prior litigation as describing optically active and substantially optically pure levofloxacin. Specifically, after an eight-week bench trial during which it was argued that the '407 patent was both anticipated and obvious over racemic ofloxacin, the claims were construed to be directed to levofloxacin that is optically active and substantially optically pure, and to exclude both racemic ofloxacin and the S(–) molecules contained in racemic ofloxacin. *Mylan*, 348 F. Supp. 2d at 723, 728-30. This construction – which formed the basis for the holdings that ofloxacin neither anticipated nor rendered obvious the claims of the '407 patent – was affirmed on appeal by the Federal Circuit. *See Ortho-McNeil Pharmaceutical Inc. v. Mylan Labs., Inc.*, 161 Fed. Appx. 944 (Fed. Cir. 2005).

Lupin has not challenged this construction here, and therefore cannot, and does not, contend that Floxin® contains what is claimed in the '407 patent – precisely the showing that Lupin must make to show that the patent term extension is invalid. *See* 35 U.S.C. § 156(a) (referring to "[t]he term of a patent which claims a product") (emphasis added). Unlike the levofloxacin claimed in the '407 patent, the S(–) molecules contained in racemic ofloxacin are neither optically active nor substantially pure because they are present together with an equal number of R(+) molecules. *See Mylan*, 348 F. Supp. 2d at 726-30. For this reason,

the product claimed in the '407 patent – levofloxacin that is optically active and substantially optically pure – was first approved in Levaquin® and meets all the requirements necessary for a patent term extension. For this reason alone, Lupin cannot prevail as a matter of law, and Plaintiffs are entitled to summary judgment.

III. The PTO and FDA Did Not Act Arbitrarily and Capriciously in Granting the '407 Patent Term Extension and Their Decisions Are Entitled To Great Deference

Lupin has identified nothing arbitrary and capricious about the PTO's decision – made in concert with the FDA – to grant the extension of the '407 patent term. Indeed, in granting the term extension of the '407 patent, the PTO acted in a manner consistent with its regular and longstanding practice. *See* PF ¶ 33 (Mossinghoff ¶ 19). Additionally, the FDA – in advising the PTO that the "active ingredient" in Levaquin® had not been approved previously – used that term in the same way that it had done for decades, in a manner consistent with its own definition (which the parties agree is controlling here) and the usage of the terms "active ingredient" and "API" by the industry – including by Lupin and Matrix Laboratories, the company that supplies the levofloxacin API to Lupin. Both agencies acted consistently with the practices and procedures enumerated in a decades-old memorandum of understanding ("MOU") and abided by longstanding practices rooted in industry and agency custom. Their decisions certainly are not arbitrary and capricious. Instead, as the Federal Circuit held in *Glaxo*, the

decisions of the PTO and the FDA "as to which patented chemical compounds fall within Congress' definition of 'products'" must be "give[n] great deference." 894 F.2d at 399 (emphasis added).

Although these arguments would apply equally to any patent covering an enantiomer of a previously approved racemate, under the specific circumstances of this case – with respect to Floxin® and Levaquin® – there are additional reasons why a patent term extension was appropriately granted. As explained below, these reasons provide far more than the "rational basis" necessary to deny Lupin's motion for summary judgment and grant Plaintiffs' cross-motion. Given the consistent practice of granting patent term extensions to patents covering enantiomers of previously approved racemates – rooted both in the underlying science and well-established industry custom – Lupin cannot possibly meet its burden of proof on this issue.

A. The PTO and the FDA Acted Consistently with Longstanding Practice

Consistent with the FDA's longstanding practice, FDA-approved product labeling and the FDA's Orange Book both list the racemate ofloxacin as the "active ingredient" in Floxin®. *See* PF ¶ 34 (Lin ¶ 25). Neither levofloxacin nor the dextrorotatory enantiomer is, or ever has been, listed as an "active ingredient" in Floxin® because neither is considered by the FDA or anyone else – save Lupin, and only for purposes of this case – to be an "active ingredient" in

Floxin®. Moreover, both the FDA and the PTO followed to the letter the MOU between the agencies that governs the agencies' cooperation in reviewing patent term extension applications. *See* PF ¶ 35 (Mossinghoff ¶ 19). Consistent with the established procedure set out in the MOU and with other instances in which the PTO and FDA have considered precisely this same question, the agencies, acting in concert, determined that the '407 patent claiming the levofloxacin enantiomer is entitled to term extension, notwithstanding the prior approval of the ofloxacin racemate in Floxin®. The decisions of the FDA and the PTO – made pursuant to long established procedure and consistent with longstanding practice – are entitled to great deference. *See supra* at Argument, Part I.

1. FDA-Approved Labeling and the FDA's Orange Book Always List the Active Ingredient in a Racemic Drug as the Racemate

Floxin® is by no means the first racemic product approved by the FDA. In fact, the FDA has approved dozens of racemates, in each case characterizing the "active ingredient" in the racemic product as a single entity – the racemate itself, distinct from its enantiomers. *See* PF ¶ 36 (Lin ¶ 20 & Ex. C). This longstanding practice is evident from the FDA-approved labeling and the FDA's Orange Book descriptions for racemic products. In each instance, without exception, both the approved product labeling and Orange Book listings for racemic drug products identify a single "active ingredient" – the racemate itself – not one or a combination of its enantiomers. *See* PF ¶ 37 (Lin ¶ 20 & Ex. C).

Even Lupin appears to have recognized the FDA's longstanding practice in this regard. For example, Lupin has submitted a citizen's petition to the FDA, requesting permission to submit an application to market a generic fexofenadine hydrochloride product. *See* PF ¶ 38 (Lin ¶ 22 & Ex. D). Fexofenadine is a racemate. *See* PF ¶ 39 (Lin ¶ 22 & Ex. D). As part of its petition, Lupin submitted proposed labeling for its generic fexofenadine product that characterizes the "active ingredient" in the drug as racemic fexofenadine – not one or both of its enantiomers. *See* PF ¶ 40 (Lin ¶ 22 & Ex. D)

2. The FDA Has Never Considered Racemates "Combination Drugs" or Regulated Them As Such

Were the FDA, contrary to its longstanding practice, to treat a racemic product as a combination of multiple active ingredients, namely its enantiomers, racemic products would be subject to a specific set of regulations, the FDA's special "combination rules," which govern the approval of drugs that contain a combination of active ingredients. *See* PF ¶ 41 (Lin ¶ 23). These "combination rules" require that the drug product sponsor conduct testing on each active ingredient individually and in combination to show the contribution of each active ingredient to the efficacy and safety of the combination product. *See* PF ¶ 42 (Lin ¶ 23 (*citing* 21 CFR § 300.50; Guidance for Industry, Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV)). The FDA, however, has *never* subjected racemates to these "combination rules" and does not require the

sponsor of racemic products to test each enantiomer individually. *See* PF ¶ 43 (Lin ¶ 23). To the contrary, the FDA will not approve a racemic product based solely on tests conducted on one or both of its individual enantiomers and will not approve an enantiomeric product based solely on tests conducted on the corresponding racemate. *See* PF ¶ 44 (Lin ¶ 21). At no time did the FDA subject Floxin® to the "combination rules" or even suggest that would be appropriate. In fact, the FDA required an entirely new NDA – based on entirely new testing – when Plaintiffs sought regulatory approval to market Levaquin®. *See* PF ¶ 45 (Lin ¶ 26). Plaintiffs were not able to rely on the testing submitted in the Floxin® NDA. *See* PF ¶ 46 (Lin ¶ 26). Therefore, under no circumstances could the approval of Floxin® be considered the "first permitted commercial marketing or use of [levofloxacin]." 35 U.S.C. § 156 (a)(5)(A) (emphasis added).

3. The Grant of a Term Extension Was Consistent with the PTO's and the FDA's Established Procedure and Longstanding Practice

Finally, the instant case is far from the only one in which a patent term extension was granted for a patent covering an enantiomeric product, notwithstanding the previous approval of the corresponding racemate. Indeed, the patent term extension process has been for more than two decades the subject of a memorandum of understanding between the PTO and the FDA, providing for

cooperation between these agencies in reviewing patent term extension applications. As the 1986 MOU explains,

> [w]hile it is the responsibility of the Commissioner of Patents and Trademarks to decide whether an applicant has satisfied these six conditions [of 35 U.S.C. §§ 156(a)(1-5) and 156(d)(1)], FDA possesses expertise and records regarding the last four and has certain direct responsibilities under 35 U.S.C. 156 for determining the length of the regulatory review period. Consequently, to facilitate eligibility decisions and permit FDA and PTO to carry out their responsibilities under 35 U.S.C. 156, the FDA and PTO have entered into this agreement.

See PF ¶ 47 (Mossinghoff ¶ 10).

Following the practice and procedure set out in the MOU, the PTO, informed by the expertise of the FDA, has over the past ten years considered at least five other applications for patent term extensions for patents covering enantiomeric products subsequent to approval of their corresponding racemates. *See* PF ¶ 48 (Mossinghoff ¶ 20) (Patent Term Extensions for U.S. Patent No. 4,738,974 on NEXIUM®; U.S. Patent No. Re. 34,712 on LEXAPRO®; U.S. Patent No. 4,911,920 on BETAXON®; U.S. Patent No. 5,362,755 on XOPENEX®; and U.S. Patent No. 4,309,445 on REDUX®). In each case, the FDA and the PTO, acting in concert, have determined that the patent covering the enantiomeric product was entitled to extension and have granted the term extension application because approval of the racemate does not constitute prior approval of the same active ingredient as in the enantiomeric product. *See* PF ¶ 49

(Mossinghoff ¶ 20). In no case have the agencies come to the contrary conclusion. *See* PF ¶ 50 (Mossinghoff ¶ 20).

The two patent term extension applications cited by Lupin are inapposite. Neither concerns a term extension for a patent claiming an enantiomeric product subsequent to FDA approval of the corresponding racemate and therefore neither involves the question presently before this Court. *See* PF ¶ 51 (Mossinghoff ¶¶ 25-26). Instead, the Symbicort® application involved a traditional "combination product" – of the sort regulated by the FDA's combination rules – comprising two active ingredients (formoterol fumarate dihydrate and budesonide), each of which had been previously approved. *See* PF ¶ 52 (Confoy, Ex. M at 3). The patent applicant argued that because Symbicort® is a "synergistic combination" it should be considered "as a single active ingredient for patent term extension purposes" and an extension should be granted. *See* PF ¶ 53 (Confoy, Ex. M at 3). The PTO found no exception in the term extension statute for "synergistic effect" and explained that the Symbicort® case was governed by the language of Section 156, which provides that the term "drug product" includes any new drug "as a single entity or in combination with another active ingredient." *See* PF ¶ 54 (Confoy, Ex. M at 3-4). Because each of the

individual active ingredients had been previously approved, the patent covering the combination product was ineligible for term extension.[8]

The Metvixia® application, also relied on by Lupin, likewise has no relevance to a term extension for a patent claiming an enantiomeric product subsequent to FDA approval of the corresponding racemate. There, the patent applicant sought extension of a patent claiming a salt of the ester, methyl aminolevulinate, even though the salt form of the corresponding non-esterified molecule, aminolevulinic acid, had been previously approved. *See* PF ¶ 55 (Confoy, Ex. N at 2). Citing the portion of 35 U.S.C. § 156 that defines "drug product" as "the active ingredient … including any salt or ester of the active ingredient," the PTO denied the application. *See* PF ¶ 56 (Confoy, Ex. N at 3) (emphasis in original). As the PTO explained, pursuant to the explicit language in 35 U.S.C. § 156, "a 'product' includes all three forms, any salt of a molecule is statutorily the same 'product' as any ester of the molecule for purposes of the patent term extension provisions in section 156." *See* PF ¶ 57 (Confoy, Ex. N at 3). As with Symbicort®, the Metvixia® application does not concern racemates or enantiomers and 35 U.S.C. § 156 does not include any language regarding

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[8] Another case that Lupin relies upon, *Arnold Partnership v. Dudas*, 362 F.3d 1338 (Fed. Cir. 2004), also concerns a combination of previously approved active ingredients and is similarly inapposite.

racemates or enantiomers – certainly nothing analogous to the "including any salt or ester" language that the PTO found dispositive in Metvixia®. In fact, as explained above, in the absence of any language in the term extension statute related to racemates and enantiomers, the policy of the PTO and FDA has been to grant patent term extension applications for patents covering enantiomeric products, notwithstanding prior approval of the corresponding racemates, *see* PF ¶ 35 (Mossinghoff ¶ 19), because it is the expert view of both agencies that they are separate products with distinct active ingredients.

The distinction between salts and esters on the one hand – which Section 156 explicitly defines as constituting the same "active ingredient" – and racemates and enantiomers on the other – about which Section 156 is silent – can be seen most clearly from the case of Nexium® and Nexium® IV. *See* Mossinghoff, Exs. R & S. Nexium® (esomeprazole magnesium) is an enantiomer and its corresponding racemate (omeprazole) had been previously approved as Prilosec®. *See* PF ¶ 58 (Mossinghoff ¶ 20). The patentee applied for a term extension under 35 U.S.C. § 156 for the patent covering Nexium®, notwithstanding the prior approval of the racemate, Prilosec®. *See* PF ¶ 59 (Mossinghoff ¶ 20). The PTO and the FDA evaluated the Nexium® patent term extension application under the MOU and, consistent with their longstanding practice, granted the term extension, finding that "the requirements of the law have

been met," *i.e.*, that prior approval of the racemic Prilosec® was not approval of the same "active ingredient" as in the enantiomeric Nexium® for purposes of 35 U.S.C. § 156. *See* PF ¶ 60 (Mossinghoff ¶ 20). A separate patent covered the intravenous version of Nexium®, Nexium® IV, and the patentee also applied for a term extension for the patent covering Nexium® IV. *See* PF ¶ 61 (Mossinghoff ¶ 27). Nexium® IV (esomeprazole sodium) is also enantiomeric, but a different salt form of Nexium® (esomeprazole magnesium). *See* PF ¶ 62 (Mossinghoff ¶ 27). The PTO and FDA denied that term extension application based on the previous approval of Nexium® and the "any salt or ester" language in 35 U.S.C. § 156. *See* PF ¶ 63 (Mossinghoff ¶ 27). The PTO made sure to point out, however, that "Nexium® IV [the enantiomer] does not have the same active ingredient as Prilosec® [the racemate]." *See* PF ¶ 64 (Mossinghoff ¶ 27) (emphasis added).

Here, consistent with the established procedure set out in the MOU, the PTO and FDA, acting in concert, determined that the '407 patent is entitled to a term extension, notwithstanding the prior approval of Floxin®. This accords with each and every other instance in which the PTO and the FDA have considered precisely the same question of whether a patent claiming an enantiomeric product is entitled to term extension following approval of the corresponding racemate. The decisions of the FDA and PTO – made pursuant to long established procedure and consistent with longstanding practice – are entitled to great deference.

B. FDA's and PTO's Approach to Racemates and Enantiomers is Firmly Rooted in Science and Longstanding Industry Practice

The FDA's and PTO's treatment of racemates and their component enantiomers as different products for purposes of patent term extensions under Section 156(a) is based on science and longstanding industry practice. Since at least 1978 – more than 6 years before the enactment of Section 156(a) – FDA regulations have defined "active ingredient" as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure of any function of the body of man or other animals." 21 CFR § 210.3(b)(7). During the subsequent nearly three-decade period, both agencies repeatedly have considered and applied this definition in the context of racemic products. As discussed *supra* (at Argument, Part III.A.1), in each case that Plaintiffs are aware of, the FDA and the PTO have concluded that the racemate – not its component enantiomers – is the "active ingredient" of the product. This is not surprising given well-established science regarding racemates and enantiomers, as well as longstanding industry practice.

1. Longstanding Industry Practice Confirms Levofloxacin is not an "Active Ingredient" in Floxin®

The standard manufacturing process used throughout the pharmaceutical industry for small molecule drugs confirms that levofloxacin and

ofloxacin are different active ingredients. This manufacturing process is divided into two distinct phases: a primary manufacturing phase and a secondary manufacturing phase. *See* PF ¶ 65 (Myerson ¶ 11). The primary manufacturing phase refers to the chemical processes used to synthesize and purify the substance – known in industry as the active pharmaceutical ingredient ("API") or simply as the active ingredient – that is intended to furnish the desired pharmacological effect. *See* PF ¶ 66 (Myerson ¶¶ 12, 14). Characterizing this substance as the API or active ingredient is entirely consistent with the FDA regulatory definition of "active ingredient" discussed above. *See* 21 CFR §§ 210.3(b)(7), 60.3(b)(2). During the secondary manufacturing process, the API is then blended with other substances, such as excipients or binders, to make the final drug product. *See* PF ¶ 67 (Myerson ¶¶ 13, 16). These two manufacturing stages are separate from one another and, in fact, usually occur at different facilities and often are performed by different companies. *See* PF ¶ 68 (Myerson ¶ 13).

According to its regulatory filings, Lupin intends to use this two phase manufacturing process for its proposed generic levofloxacin product. *See* PF ¶ 69 (Myerson ¶ 17). The first manufacturing phase – which results in the API – will be performed by another company, Matrix, which specializes in the manufacture of APIs. *See id.* Matrix will then deliver the API – levofloxacin – to Lupin, which will perform the secondary manufacturing phase, *i.e.*, combining the levofloxacin

with inactive ingredients to create the final drug product. *See* PF ¶ 70 (Myerson ¶ 17).

A similar two-phase manufacturing process also is used to manufacture Floxin® and Levaquin®. *See* PF ¶ 71 (Myerson ¶ 18). For Floxin®, the primary manufacturing phase results in the purified active ingredient, ofloxacin, which is then blended during the second phase with excipients to produce the final product Floxin®. *See* PF ¶ 72 (Myerson ¶ 18). Conversely, during the manufacture of Levaquin®, the primary phase results in the purified active ingredient, levofloxacin, which is then blended with excipients during the second phase to produce Levaquin®. *See* PF ¶ 73 (Myerson ¶ 18).

From the pharmaceutical manufacturing perspective, levofloxacin is not an API or "active ingredient" in ofloxacin. *See* PF ¶ 74 (Myerson ¶ 19). The "active ingredient" – the end product of the primary manufacturing process – in Floxin® is ofloxacin; whereas the "active ingredient" in Levaquin® is levofloxacin.[9] *See id.* Moreover, Lupin's and Matrix's own publicly available

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[9] Lupin raises the "legal issue" of whether levofloxacin is "an" active ingredient. Lupin Br. at 14. Of course, there is no issue, legal or otherwise, as to whether levofloxacin is "an" active ingredient in the abstract. The test is not whether levofloxacin is an active ingredient in the abstract, but whether it is an active ingredient in the previously approved Floxin® – which it is not.

materials support this conclusion. For example, until last month, Lupin's own website advertised the various APIs that it supplies. *See* PF ¶ 75 (Myerson ¶ 20). Although Lupin listed mandelic acid – a racemate – as an API, it also listed both enantiomers of mandelic acid as separate APIs. *See* PF ¶ 76 (Myerson ¶ 20 & Ex. E). Thus, Lupin itself recognizes a racemate as a stand-alone active ingredient and its component enantiomers as stand-alone active ingredients.[10] *See id.* Similarly, as discussed *supra* (at Argument, Part III.A.1), Lupin submitted a Citizen Petition to the FDA regarding its application for a generic fexofenadine HCL product in which it described the active ingredient as the racemate fexofenadine, not its enantiomers. *See* PF ¶¶ 38-40 (Lin ¶ 22 & Ex. D).

2. Undisputed Science also Confirms Levofloxacin is not an "Active Ingredient" in Floxin®

From clinical, pharmacology, microbiology and medicinal chemistry perspectives, ofloxacin and levofloxacin are entirely different therapeutic agents. As the FDA and the PTO – the two agencies with scientific expertise charged with

[10] Matrix – the provider of the levofloxacin API to Lupin – also lists on its website the APIs it manufactures. *See* PF ¶ 77 (Myerson ¶ 21 & Ex. G). The list contains nine racemates that are listed as active ingredients without any reference to their enantiomers and four enantiomers that are listed as active ingredients without any reference to the racemates. *See* PF ¶ 78 (Myerson ¶ 21 & Ex. G). Thus, Matrix and Lupin both indicate in their publicly available materials their agreement with the industry understanding that racemates themselves – not their component enantiomers – constitute active ingredients.

making determinations under Section 156(a) – have concluded, it is scientifically incorrect to characterize an enantiomer (levofloxacin) as an "active ingredient" in a corresponding racemic compound (ofloxacin).

a) Levofloxacin and ofloxacin are different drugs from the clinical, pharmacology and microbiology perspectives

It is a matter of undisputed fact that from the clinical, pharmacology and microbiology perspectives, levofloxacin and ofloxacin are different drugs. As Dr. George Zhanel, a leading researcher in the anti-infective field, points out in his declaration, levofloxacin differs from ofloxacin in many ways. *See* Zhanel, Section IV (¶¶ 29 *et seq.*). For example, levofloxacin is effective at treating community acquired respiratory infections, including those caused by penicillin-resistant *Streptococcus pneumoniae*, whereas ofloxacin is inferior at treating these and many other infections. *See* PF ¶ 79 (Zhanel ¶¶ 29-31 & 37-45). The pharmacodynamics of levofloxacin – *i.e.*, the nature of its effect on microorganisms – are different from, and superior to, ofloxacin's. *See* PF ¶ 80 (Zhanel ¶¶ 32-36). Levofloxacin differs from ofloxacin in its effects on resistant microorganisms and in its likelihood of developing resistance in microorganisms – and, again, it is superior to ofloxacin in both respects. *See* PF ¶ 81 (Zhanel ¶¶ 46-54).

Levofloxacin is also a safer drug than ofloxacin. *See* PF ¶ 82 (Zhanel ¶¶ 55-59). As Dr. Zhanel points out, it has the highest therapeutic index (the ratio

between its effective dose and the toxic dose) of any quinolone and has lower central nervous system toxicity than ofloxacin. *Id*. These characteristics allow for higher dosing of levofloxacin than ofloxacin, which can convey important clinical benefits. *See* PF ¶ 83 (Zhanel ¶¶ 56-59).

The far greater solubility of levofloxacin also makes it a different drug than ofloxacin from a clinical and pharmacological perspective. *See* PF ¶ 84 (Zhanel ¶¶ 60-63). Solubility is important to a drug's dissolution, absorption, and bioavailability, all of which influence a drug's effectiveness and toxicity. *See id*. Dr. Zhanel's declaration explains these concepts and notes his opinion that levofloxacin's superior solubility is one of the most important reasons why levofloxacin is a different and better drug than ofloxacin. *See id*.

Finally, levofloxacin and ofloxacin act differently on a molecular level. *See* PF ¶ 85 (Zhanel ¶¶ 64-72). Based on preclinical (animal), laboratory, and human clinical studies, the evidence is that the enantiomers of ofloxacin do not act separately when administered, but instead interact with each other and both interact with the drug binding site. *See id*. This evidence is consistent with the observed clinical properties of levofloxacin and ofloxacin, and reinforces the fact that ofloxacin is a single active ingredient that acts differently from levofloxacin. *See* Zhanel ¶ 72.

b) Levofloxacin and ofloxacin are different drugs from the medicinal chemistry perspective

From a medicinal chemistry perspective, levofloxacin and ofloxacin are both different compounds and different drugs. As Professor Mark Wentland, a leading quinolone medicinal chemist, explains in his declaration, ofloxacin is not a naturally occurring compound, but is synthesized in the laboratory and consists of two enantiomers that cannot be physically separated from each other because the enantiomers are tightly bound together; accordingly, medicinal chemists view a material like ofloxacin (a racemate) to be a single compound that is different from the pure forms of its individual enantiomers. *See* PF ¶ 86 (Wentland ¶¶ 24-32). Indeed, racemates have many different chemical and physical characteristics from their individual enantiomers. *See* PF ¶ 87 (Wentland ¶ 29).

Professor Wentland's declaration also reviews the literature on how quinolones, and ofloxacin and levofloxacin in particular, interact with the binding site when they act on microorganisms. *See* Wentland ¶¶ 35-49. The evidence shows that the (S) and (R) enantiomers of ofloxacin interact with each other to form a stable complex at the binding site. *See* PF ¶ 88 (Wentland ¶ 39). Accordingly, Professor Wentland concludes that ofloxacin and levofloxacin differ in their interactions with the receptor site. *See* Wentland ¶ 39. This is further proof that ofloxacin is a single active ingredient that is different from levofloxacin.

From the perspective of a medicinal chemist, the fact that ofloxacin and levofloxacin are different compounds is sufficient to end the argument as to whether Floxin® and Levaquin® are different drugs – they are. *See id*. at ¶ 33. The active ingredient of Floxin® is ofloxacin, and the active ingredient of Levaquin® is levofloxacin. *See id.*

C. There Is No Inconsistency In Granting Term Extensions for Patents That Do Not Cover New Chemical Entities

To the extent Lupin argues that because levofloxacin does not qualify as a "new chemical entity" for purposes of non-patent, regulatory exclusivity, it also is not a new "active ingredient" for purposes of the patent term extension statute, Lupin is mistaken. Lupin appears to be advancing the very argument rejected by the Federal Circuit in *Glaxo v. Quigg* – that "active ingredient" is equivalent to "new chemical entity" or "active moiety." As *Glaxo* held, however, "active ingredient" is – as Lupin elsewhere concedes (*see* Lupin Mem. at 15) – a commonly used term. In 1984, when Hatch-Waxman was enacted, it meant then what it does now: a component "intended to furnish pharmacological effect . . .", 21 CFR § 210.3(b)(7) – not "new chemical entity" as that term is used for purposes of non-patent, regulatory exclusivity. *See Glaxo*, 894 F.2d at 399 and n.10 ("Congress specifically selected terms with narrow meanings that it chose from among many alternatives, [f]or example: 'new molecular entity,' 'active moiety,' or 'new chemical entity.'").

As discussed *supra* (at footnote 6), any reliance on *Pfizer*, 359 F.3d 1361, is misplaced. Apart from the fact that the *Pfizer* decision cannot overrule *Glaxo*, the *Pfizer* court was focused on a different question from the one presently before this Court. Thus, the publication cited in *Pfizer*, Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (F.D.A. Oct. 3, 1994), is directed to non-patent exclusivity provisions, not to patent term extensions under Section 156. Indeed, the FDA itself makes clear that "active ingredient" is not synonymous with "active moiety" for purposes of Section 156. For example, in the "Frequently Asked Questions on the Patent Term Restoration Program" section on the FDA website, the FDA states:

> **7. How is active ingredient defined with regard to the first permitted commercial marketing or use of the product**? Permission for commercial marketing or use must be the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred. A product is the active ingredient[] contained therein for patent term extension purposes. Active ingredient does not equal active moiety (generally the molecule or ion responsible for the physiological or pharmacological action).

See http://www.fda.gov/cder/about/smallbiz/patent_term.htm (last visited October 21, 2008) (emphasis added).[11]

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[11] Lupin's reliance on *Fisons v. Quigg*, 1988 WL 150851 (D.D.C. Aug. 19, 1988) ("Fisons I"), is likewise misplaced. In *Fisons I*, the patent holder argued that "product" in Section 156 should not be limited only to "active ingredient" as he (continued…)

Moreover, while superficially similar to the provisions governing patent term extensions, the statute governing non-patent, regulatory exclusivity for new chemical entities has a different scope. *See* 21 U.S.C. § 355(c)(3)(E)(ii). For this reason, it is not surprising that it has been interpreted differently by the FDA from the statutory provisions governing patent term extensions. Nor is it surprising that the FDA has in some instances refused to accord enantiomers of previously approved racemates five-year regulatory exclusivity, while nonetheless certifying that the approval of an enantiomer of a previously approved racemate represents the first approval of that active ingredient for purposes of patent term extension requests.

Finally, Lupin is factually incorrect that the FDA universally has refused to accord five-year regulatory exclusivity to enantiomers of previously approved racemates. In a 1997 Federal Register notice, the FDA considered a revision of its policy, to encourage medically significant innovation, but it never completed its rulemaking. 62 Fed. Reg. 2167 (Jan 15, 1997). Instead, its

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sought term extensions on patents covering new uses or dosages of the same active ingredient. *Id*. at *1. The court correctly held that Congress "restrictively define[d] 'product' for purposes of Section 156 as the drug's active ingredient." *Id*. at *7. That the *Fisons I* court appeared to conflate "new chemical entity" with "active ingredient" is of no moment, since the Federal Circuit in *Glaxo* established that "active ingredient" has its ordinary meaning and does not mean "new chemical entity."

rulemaking effort was superseded by Congress, which – as part of the Food and Drug Administration Amendments Act of 2007 – resolved a longstanding dispute about the proper treatment of enantiomers of previously approved racemates for purposes of regulatory exclusivity by permitting enantiomers to be treated as new chemical entities under certain circumstances. *See* Pub. L. No. 110-85, 121 Stat. 823 (2007); FDAAA § 1113.

In any event, Lupin's inapt analogy to the language of non-patent regulatory exclusivity provisions – irrelevant under *Glaxo* – is a far cry from clear and convincing evidence that the PTO and the FDA acted arbitrarily and capriciously in granting a term extension to the '407 patent. Rather, the PTO's decision to grant the patent term extension in the instant case – made in concert with the FDA – is fully consistent with the longstanding practice of the agencies and industry, accords with the agencies' decisions in each and every other instance in which they considered precisely the same question and is strongly supported by the science as a matter of undisputed fact.

CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that the Court deny Lupin's motion for summary judgment and instead grant summary judgment in favor of Plaintiffs.

Respectfully submitted,

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